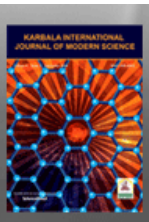

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Vitamin D3 Toxicity-Induced Hypercalcemia in Staphylococcal Arthritis: A Focus on IL-6

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Abstract

Background: Vitamin D3 over-supplementation can induce toxicity through the development of hypercalcemia and may disturb immune modulation. This study examines the relationship between hypercalcemia resulting from Vitamin D3 Overdose and serum Interleukin-6 (IL-6) levels in patients diagnosed with *staphylococcal* arthritis.

Methods: Forty male patients (mean age: 31 years; range: 17–45 years) were enrolled from Dec. 2024 to Feb. 2025. Twenty cases of staphylococcal arthritis were compared with twenty healthy male controls. Serum concentrations of Vitamin D3, calcium, IL-6, and other biochemical markers (urea, creatinine, ESR, WBC, and potassium) were analyzed. *Staphylococcus aureus* was isolated from synovial fluid and confirmed using the Vitek 2 system.

Results: Vitamin D3 levels were significantly elevated in patients (498.95 ± 247.43 ng/mL) compared to controls (34.6 ± 17.7 ng/mL, $p < 0.001$). Calcium levels were also significantly higher in the patient group (15.72 ± 2.61 mg/dL) compared to the control group (9.2 ± 0.5 mg/dL, $p < 0.001$). Conversely, IL-6 levels were markedly reduced in patients (4.07 ± 2.02 pg/mL) compared to controls (10.2 ± 1.3 pg/mL, $p < 0.001$), indicating an immunosuppressive profile. Other laboratory markers (urea, creatinine, ESR, WBC, potassium) also showed statistically significant differences ($p < 0.05$). Pearson correlation revealed a strong negative association between Vitamin D3 and IL-6 levels ($r = -0.97$).

Conclusion: The findings demonstrate that Vitamin D3 overdose, resulting in hypercalcemia, significantly suppresses IL-6 expression in patients with staphylococcal arthritis. This suppression is mediated indirectly through hypercalcemia rather than a direct effect of Vitamin D3. Therefore, careful monitoring and individualized dose adjustment are recommended to prevent toxicity and associated immune dysregulation

Keywords

Vitamin D3; toxicity; Interleukin-6; hypercalcemia; staphylococcal arthritis

Cover Page Footnote

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RESEARCH PAPER

Vitamin D3 Toxicity-induced Hypercalcemia in *Staphylococcal* Arthritis: A Focus on IL-6

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Conclusion: **The findings demonstrate that Vitamin D3 overdose, resulting in hypercalcemia, significantly suppresses IL-6 expression in patients with staphylococcal arthritis. This suppression is mediated indirectly through hypercalcemia rather than a direct effect of Vitamin D3. Therefore, careful monitoring and individualized dose adjustment are recommended to prevent toxicity and associated immune dysregulation.**

Keywords: Vitamin D3, Toxicity, Interleukin-6, Hypercalcemia, *Staphylococcal* arthritis

1. Introduction

1.1. Vitamin D3 physiology

Vitamin D3 (cholecalciferol) plays a crucial role in maintaining calcium homeostasis and promoting bone mineralization. Beyond skeletal health, it also regulates various cellular functions, including cell proliferation, differentiation, and immune modulation. Vitamin D deficiency is one of the most prevalent global micronutrient deficiencies and is linked to extra-skeletal conditions such as hypertension, metabolic syndrome, obesity, COPD, and immune dysregulation [1]. Serum levels <20 ng/mL indicate deficiency, while 21−29 ng/mL is considered insufficient [2].

1.2. Toxicity risks

The global awareness of vitamin D deficiency has led to widespread unsupervised supplementation. Consequently, cases of Vitamin D toxicity (hypervitaminosis D), typically caused by excessive oral intake rather than sunlight exposure, have increased [3]. Toxicity is characterized by hypercalcemia, suppressed parathyroid hormone (PTH), and

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elevated urinary calcium levels (>150 ng/mL), often associated with high serum 25(OH)D levels. Historical reports from the 1940s to the 1950s documented hypercalcemia outbreaks linked to mass vitamin D fortification, particularly in Europe [4,5].

1.3. Link to immune modulation

In addition to its fundamental role in calcium metabolism, Vitamin D3 acts as a key modulator of the immune response [6–8]. However, excessive calcium levels (hypercalcemia) resulting from Vitamin D3 toxicity can disrupt immune homeostasis. Hypercalcemia has been reported to impair various immune functions, including T-cell activation, proliferation, cytokine secretion, B-cell antibody production, and macrophage phagocytic activity [7,8]. This immunosuppressive effect contributes to increased vulnerability to bacterial, viral, and fungal infections [7]. Furthermore, hypercalcemia may suppress interleukin-6 (IL-6), a cytokine essential for both acute and chronic inflammatory responses [9]. Proposed mechanisms for this suppression include activation of the calcium-sensing receptor (CaSR), which inhibits NF-κB signaling; mitochondrial dysfunction leading to oxidative stress; and direct interference with JAK-STAT signaling pathways [10,11]. Disruption of IL-6 signaling may compromise both innate and adaptive immunity, resulting in reduced antibody production, impaired neutrophil responses, and an increased risk of infection [8,11].

1.4. Study aim

In this context, the present study aims to investigate the toxicological and immunomodulatory effects of Vitamin D3 in a *staphylococcal* arthritis model. Specifically, it examines the relationship between elevated serum Vitamin D3 levels, which can result in hypercalcemia, and the down-regulation of IL-6 in affected patients. The study also aims to investigate the broader immunosuppressive effects of excessive Vitamin D3 intake. By utilizing a well-defined cohort of patients with *Staphylococcus aureus* arthritis and matched healthy controls, the research aims to provide novel insights into the immune-modulating effects of unregulated Vitamin D3 supplementation.

1.5. Ethics approval

This study was reviewed and approved by the Research Ethics Committee of the College of Science, University of Kerbala (Approval Number: 0013CSE; Approval Date: 30-12-2024). All procedures involving human participants were conducted by the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical principles.

Written informed consent was obtained from all individual participants included in the study prior to sample collection. The study adhered to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, with careful consideration of participant age and sex. Privacy and confidentiality of all participant data were strictly maintained throughout the research process.

2. How does vitamin D toxicity occur?

Vitamin D toxicity (VDT), also known as hypervitaminosis D, is a rare but potentially serious condition resulting from prolonged excessive intake of vitamin D. It is most commonly attributed to over-supplementation rather than excessive sun exposure. Although ultraviolet B (UVB) radiation stimulates endogenous vitamin D production, fortified foods typically contribute only modest amounts [1]. VDT is characterized by hypercalcemia, hypercalciuria, suppressed or undetectable parathyroid hormone (PTH) activity, and elevated levels of 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$), often exceeding 150 ng/mL. Clinical manifestations primarily stem from hypercalcemia and may include nonspecific symptoms such as fatigue, confusion, and gastrointestinal distress. Serum 25(OH)D concentrations above 150–200 ng/mL are generally indicative of toxicity [12]. Certain conditions, such as idiopathic infantile hypercalcemia, Williams–Beuren syndrome, granulomatous disorders, and certain lymphomas, can increase sensitivity to vitamin D; however, most healthy individuals can tolerate levels up to 100 ng/mL without adverse effects [13]. Most current knowledge of VDT is derived from animal studies, clinical case series, and isolated case reports. Human trials are scarce due to ethical constraints. Between the 1930s and 1950s, public health initiatives in the United States and the United Kingdom promoted vitamin D fortification to prevent rickets and enhance overall bone health. In the 1940s, extremely high doses of vitamin D (200,000–300,000 IU/day) were used therapeutically to treat tuberculosis and rheumatoid arthritis. However, a surge in hypercalcemia cases—particularly in the United Kingdom—led to the discontinuation of vitamin D fortification. Following early detection of hypercalcemia, fortification programs were halted, and symptoms of

toxicity resolved within months. This historical episode underscored the potential hazards of excessive vitamin D intake and remains a relevant public health concern [4,5]. At that time, no reliable assays were available to measure vitamin D or its metabolites; thus, diagnosis of hypercalcemia in some cases relied on dietary history [14].

2.1. Mechanisms of vitamin D toxicity

Vitamin D toxicity (VDT) is believed to result from excessive accumulation of vitamin D metabolites that bind to the vitamin D receptor (VDR) within the nucleus of target cells, thereby activating gene expression. Three primary mechanisms have been proposed to explain this toxicity [15].

1. Elevated intracellular $1,25(OH)_2D$ levels:

Toxicity may involve an increase in intracellular concentrations of 1,25-dihydroxyvitamin D (the hormonally active form of vitamin D). Although most studies have reported normal or slightly elevated levels in cases of VDT, Mewar et al. documented abnormally high levels, suggesting this as a possible mechanism in specific contexts.

2. Saturation and displacement of vitamin D-binding protein (DBP):

$1,25(OH)_2D$ binds strongly to the VDR but has a relatively weak affinity for DBP—the main transport protein. During hypervitaminosis D, the accumulation of vitamin D metabolites can exceed the binding capacity of vitamin D-binding protein (DBP). As a result, unbound active or precursor forms (particularly 25(OH)D, which has a high affinity for the VDR) may freely enter cells and activate transcriptional responses inappropriately [16].

3. Accumulation of multiple vitamin D metabolites beyond DBP capacity:

Excessive intake of vitamin D leads to elevated serum levels of both vitamin D3 and 25-hydroxyvitamin D (25(OH)D). This, in turn, increases the production of various metabolites such as 25(OH)D_3, $24,25(OH)_2D_3$, $25,26(OH)_2D_3$, and $25(OH)D_3$-26,23-lactone. When the cumulative concentration of these metabolites exceeds the binding capacity of DBP, free $1,25(OH)_2D_3$ becomes available in circulation. This unbound form can enter target cells and aberrantly stimulate VDR-mediated transcription. Several studies on vitamin D intoxication support this mechanism as a contributing factor in toxicity [17].

2.2. Diagnostic of hypervitaminosis D

The diagnosis of vitamin D toxicity (VDT) relies on a thorough clinical and pharmacological history. Most cases involve patients receiving high-dose vitamin D supplementation, often for conditions such as osteoporosis, hyperparathyroidism, hypophosphatemia, osteomalacia, or renal osteodystrophy. In recent years, vitamin D has also been widely used in otherwise healthy individuals due to its perceived protective effects against a broad range of diseases. Primary care providers should exercise caution when managing patients receiving vitamin D or its analogs, especially in populations with underlying granulomatous diseases or lymphomas, where hypercalcemia may present more aggressively [5,14]. VDT can be distinguished from other causes of hypercalcemia using modern biochemical assays, including serum levels of intact parathyroid hormone (PTH), 25-hydroxyvitamin D [25(OH)D], and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. In symptomatic cases, laboratory findings typically show elevated serum and urinary calcium, suppressed intact PTH, 25(OH)D levels exceeding 100 ng/mL, and standard or decreased $1,25(OH)_2D$ concentrations [12].

2.3. Vitamin D3 poisoning causes hypercalcemia, which disrupts the immunological system

Vitamin D3 toxicity leads to hypercalcemia—an abnormal elevation of blood calcium levels. While Vitamin D3 plays a crucial role in promoting intestinal calcium absorption and maintaining bone health, excessive intake can disrupt calcium homeostasis and subsequently impact immune system function [6].

Over-supplementation enhances intestinal calcium absorption and stimulates calcium release from the bone, resulting in increased plasma calcium concentrations. In some instances, such as coexisting hypertension, this effect may be exacerbated by enhanced bone resorption [7].

Hypercalcemia has been shown to impair key immunological functions. It interferes with T-cell activation, proliferation, and cytokine production, thereby compromising the adaptive immune response. T cells are critical for identifying and eliminating pathogens; their dysfunction weakens host defenses. Similarly, elevated calcium levels can impair B-cell maturation and antibody production, undermining humoral immunity [8]. Macrophage function, especially phagocytosis of invading pathogens, may also be suppressed in hypercalcemic conditions.

As a result, hypercalcemia induced by Vitamin D3 toxicity contributes to a heightened susceptibility to bacterial, viral, and fungal infections due to concurrent impairments in T cells, B cells, and macrophages [6,8].

2.4. IL-6 disruption and hypercalcemia

Hypercalcemia, characterized by high blood calcium levels, can impact numerous physiological processes. Hypercalcemia disrupts IL-6 production, which is essential for immunological response and inflammation. This review examines how hypercalcemia impairs IL-6 formation and signaling and how it may affect numerous organ systems [9]. Malignancy, hyperparathyroidism, and some medicines can cause metabolic hypercalcemia. While hypercalcemia affects calcium homeostasis, its effects on the immune system are less well understood. The multifunctional cytokine IL-6 is essential for hematopoiesis, inflammation, and immunological responses [18]. A new hypothesis suggests that hypercalcemia disrupts IL-6 synthesis and signaling, causing a chain of downstream consequences [11]. Research is ongoing to determine how hypercalcemia impairs IL-6. However, many approaches have been proposed. Calcium-sensing receptor stimulation Involves High calcium levels activating the CaSR, a G protein-coupled receptor found on many cell types, including immune cells. CaSR activation may decrease NF-κB signaling, which affects IL-6 gene expression [10,19]. Mitochondrial dysfunction: Oxidative stress and ROS generation increase with hypercalcemia due to mitochondrial malfunction.

Additionally, ROS can hinder IL-6 synthesis and impair the NF-κB signaling pathway. Finally, direct IL-6 signaling effects: The direct interaction between hypercalcemia and IL-6 signaling pathways, especially the JAK-STAT pathway, may reduce downstream responses [11]. IL-6 disruption in hypercalcemia can decrease immunological response: Both innate and adaptive immune responses depend on IL-6. Due to its disturbance, infection risk, antibody production, and neutrophil function can decrease [8]. Although IL-6 is often associated with acute inflammation, it also plays a role in chronic inflammation. Hypercalcemia may exacerbate chronic inflammatory disorders due to an imbalance in IL-6 [18]. Bone degeneration Disrupting IL-6 can increase bone resorption and decrease bone growth, contributing to osteoporosis [20,21].

3. Materials and methods

3.1. Patients and samples

A total of 40 participants were recruited from Jood Specialist Laboratory (Hillah, Iraq) between Dec. 2024 to Feb. 2025. The study group comprised 20 male patients (mean age: 31 years; range: 17–45 years) diagnosed with staphylococcal arthritis who had been receiving oral Vitamin D3 supplementation (50,000 IU weekly) for at least eight consecutive weeks prior to sample collection [3]. The control group included 20 age-matched healthy male volunteers with no history of Vitamin D3 supplementation. These controls provided baseline reference values for biochemical and immunological comparisons. Patients with staphylococcal arthritis were specifically selected due to their active infection and immune engagement, making them suitable for evaluating the immunomodulatory effects of Vitamin D3. Blood samples were collected using serum and EDTA tubes. Serum samples were used to assess Vitamin D3, total calcium (Ca), potassium (K), parathyroid hormone (PTH), and interleukin-6 (IL-6) levels. EDTA-anticoagulated samples were analyzed for white blood cell (WBC) count and erythrocyte sedimentation rate (ESR). Synovial fluid was aspirated from infected joints and subjected to microbiological analysis. *Staphylococcus aureus* was isolated using conventional culture techniques and identified via the VITEK 2 system. Although all patients had been prescribed Vitamin D3 to improve bone health, serum Vitamin D3 concentrations had not been routinely monitored during the supplementation period preceding enrollment in this study.

4. Results

4.1. Isolation and identification

The presence of *staphylococci* within the lesion should be assumed upon examination of direct Gram staining and should be cultured before that. The organism is isolated by spreading material from the clinical specimen (Synovial Fluid) over a solid medium, such as blood agar, tryptic soy agar, or heart infusion agar. Specimens likely to be contaminated with other microbes are plated on a medium containing mannitol salt and 7.5 % sodium chloride, over which halo-tolerant *staphylococci* can grow. Ideally, Gram staining of the colony should be conducted, and tests for the production of catalase and coagulase should be performed, by which the

coagulase-positive S aureus should be identified rapidly. After that, the ideal bacterial isolate should be verified using the VITEK 2 system.

4.2. Statistical interpretation

As shown in Table 1, serum vitamin D3 levels were significantly elevated in patients with staphylococcal arthritis (498.95 ± 247.43 ng/mL) compared to healthy controls (34.6 ± 17.7 ng/mL), with a *p-value* < *0.001*. Similarly, total calcium concentrations were markedly higher in the patient group (15.72 ± 2.61 mg/dL) than in the control group (9.2 ± 0.5 mg/dL), $p < 0.001$. In contrast, IL-6 levels were significantly lower in patients (4.07 ± 2.02 pg/mL) compared to controls (10.2 ± 1.3 pg/mL), also with a *p-value* < *0.001*. Additional biochemical markers, including urea, creatinine, ESR, WBC count, and serum potassium, showed statistically significant differences between groups ($p < 0.05$).

4.3. Significant differences

Additional biomarkers showed statistically significant differences ($p < 0.05$) between patient and control groups. Specifically, the average Urea level was higher in patients (62.35 ± 26.18 mg/dL) than in controls (25.6 ± 11.4 mg/dL), and the Creatinine level was also higher (2.43 ± 1.33 mg/dL vs 0.87 ± 0.24 mg/dL). Interestingly, the erythrocyte sedimentation rate (ESR) was lower in patients (3.66 ± 0.61 mm/h) than in controls (5 ± 0 mm/h). White blood cell (WBC) counts were also lower in the patient group (3.87 ± 0.49 × 10^9/L) than in the control group (6.3 ± 1.4 × 10^9/L). Risk factors for renal toxicity, such as low serum potassium values, could be a more accurate risk calculator. In contrast, there was no statistically significant difference in parathyroid hormone (PTH) levels ($p = 0.12$), with the group mean (17.85 ± 13.66 pg/mL) for patients being less than that for controls (26.1 ± 12.5 pg/mL).

4.4. Interpretation of correlations

A strong inverse correlation was identified between serum IL-6 levels and vitamin D3 concentrations in the patient group ($r = -0.97$), as demonstrated in Fig. 1. Similarly, calcium ($r = -0.98$), creatinine ($r = -0.92$), and urea ($r = -0.89$) levels also exhibited strong negative correlations. These results indicate that higher levels of these biochemical markers in the

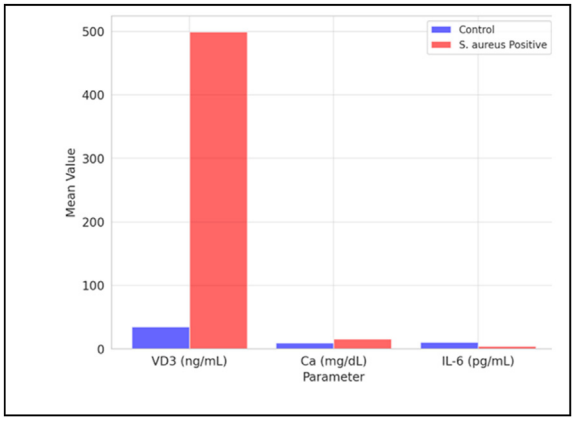

Fig. 1. Correlation between vitamin D, calcium, and interleukin 6 in comparison with the control.

Table 1. The significant and correlation value between parameters.

Parameter	Control Mean ± S. D	*S. aureus* $^+$ve Mean ± S. D	*p-value*	Sign	r=
Urea mg/dL N.V (15–45)	25.6 ± 11.4	62.35 ± 26.18	<0.001	Sig	−0.89
Creatinine mg/dL N.V (0.7–1.4)	0.87 ± 0.24	2.43 ± 1.33	<0.001	Sig	−0.92
VD3 ng/mL N.V (30–70)	34.6 ± 17.7	498.95 ± 247	<0.001	Sig	−0.99
PTH pg/mL N.V (15–65)	26.1 ± 12.5	17.85 ± 13.66	0.12	Not Sig	0.12
Ca total mg/dL N.V (8–10)	9.2 ± 0.5	15.72 ± 2.61	<0.001	Sig	−0.98
ESR mm/hr N.V (0–20)	5 ± 0	3.66 ± 0.61	<0.001	Sig	−0.87
WBC10^9/L N.V (4.5 to 11.0)	6.3 ± 1.4	3.87 ± 0.49	0.002	Sig	−0.86
IL-6 pg/mL N.V (≤43.5)	10.2 ± 1.3	4.065 ± 2.017	<0.001	Sig	−0.97
K+ mEq/L N.V (3.6–5.5)	4.1 ± 0.4	3.66 ± 0.61	0.02	Sig	−0.90

N.V = Normal value.

patient group are consistently associated with reduced IL-6 expression. In contrast, parathyroid hormone (PTH) levels showed a weak positive correlation with bone loss parameters ($r = 0.12$), indicating a minimal association in this context.

5. Discussion

5.1. Interpretation of findings

The findings reveal a significant relationship between Vitamin D3 toxicity and immune dysregulation in the context of staphylococcal arthritis. Elevated serum levels of Vitamin D3 (498.95 ± 247.43 ng/mL) and calcium (15.72 ± 2.61 mg/dL) were accompanied by a substantial reduction in IL-6 levels (4.07 ± 2.02 pg/mL, $p < 0.001$). This pattern suggests that hypercalcemia may contribute to the downregulation of IL-6 production, thereby impairing immune function. These results align with existing literature demonstrating that hypercalcemia interferes with cytokine synthesis by disrupting immune signaling pathways, particularly those associated with IL-6 activity [9–11].

5.2. Supportive evidence

Several citations in the present study support the immunosuppression associated with hypercalcemia. Hypercalcemia has been documented to suppress IL-6 production [9] via the calcium-sensing receptor (CaSR), which is followed by the downregulation of NF-κB, a key factor in IL-6 gene transcription [10]. Moreover, the hypercalcemia-mediated impact on mitochondria leads to enhanced oxidative stress, which in turn attenuates IL-6 expression [9,11]. In addition, vitamin D3 toxicity has been reported to directly affect responses in immune pathways, such as IL-6 signaling, by binding to vitamin D receptors and triggering a downstream signaling cascade [7,16,17,22].

The mechanism for this suppression of IL-6 requires further elucidation, although this study notes a significant decrease in IL-6 levels in patients with vitamin D3-induced hypercalcemia. Current findings, along with the highly significant inverse relationship between serum calcium and IL-6 ($r = -0.97$), suggest that systemic immune modulation—especially IL-6 inhibition—is likely secondary to hypercalcemia rather than a direct immunosuppressive mechanism of vitamin D3. Studies also link increased calcium with reduced IL-6 production through the activation of the calcium-sensing receptor (CaSR), which degrades the NF-κB pathway, and mitochondrial dysfunction that exacerbates oxidative stress and impairs cytokine production [9–11]. However, a physical interaction between high-dose vitamin D3 and VDR in immune cells, causing downstream transcriptional modulation, cannot be entirely disregarded [16]. Additional mechanistic studies are needed to better clarify these pathways.

5.3. Contradictory evidence

Despite our findings, previous studies have reported elevated IL-6 concentrations during hypercalcemic states [5]. IL-6 is also known to be increased in tumor-associated hypercalcemia [4] and in acute bacterial infections, including staphylococcal arthritis [23–25]. These conflicting results may stem from differences in underlying pathogenesis, immune status, or the phase of disease progression. In contrast, our findings suggest that chronic vitamin D3 overdose may promote an immunosuppressive profile rather than an inflammatory one—distinct from the IL-6 elevation typically observed in acute infection-associated hypercalcemia [26].

5.4. Dual role of IL-6 in immunity

IL-6 is a pleiotropic cytokine that mediates both proinflammatory and anti-inflammatory functions. It is a proinflammatory cytokine that induces the Acute Phase Response and promotes neutrophil recruitment. However, it also regulates immune homeostasis by acting on IL-10 and suppressing the production of TNF-α and IL-1β [15,16]. Its downregulation in our patients may impair host defense against pathogens like *S. aureus,* even though IL-6 is frequently increased in *staphylococcal* infection [24,25]. Additionally, IL-6 plays a vital role in Ulcerative colitis [19]. Therefore, the observed suppression indicates impaired immune responses, possibly resulting from stimulation by hypercalcemia or overactivation of the vitamin D receptor. The role of IL-6 and other cytokines in bone turnover disorders is well known, thus further associating immune derangement with osteopenia and osteoporosis [20].

5.5. Clinical and public health implications

The findings of this study carry important clinical and public health implications. They highlight the need for caution when prescribing high-dose vitamin D3, particularly in the absence of routine monitoring of serum calcium and inflammatory markers such as IL-6 [3,12,22]. Excessive supplementation leading to hypercalcemia may suppress immune function and increase the risk of opportunistic infections,

especially in joints where *Staphylococcus aureus* commonly colonizes [6,8]. Clinical guidelines should emphasize the importance of individualized vitamin D3 supplementation, supported by appropriate laboratory monitoring, to prevent toxicity [3,17]. The unsupervised use of over-the-counter vitamin D supplements should be strongly discouraged [12,22]. Our previous findings also indicate that changes in estrogen and glucocorticoid levels under hypercalcemic conditions may contribute to bone metabolic disturbances [20,21]. These observations reinforce the necessity of personalized dosing strategies and close patient follow-up in clinical settings.

6. Conclusion

This study highlights a strong association between vitamin D3 overdose, resulting in hypercalcemia, and the downregulation of IL-6 in patients with staphylococcal arthritis. Our findings suggest that IL-6 suppression is more likely driven by secondary effects of hypercalcemia rather than a direct immunomodulatory action of vitamin D3. These results underscore the importance of closely monitoring and adjusting vitamin D3 supplementation to prevent toxicity and minimize the risk of immunological disturbances.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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